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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/827,023	BLAZAR ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/22/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *12-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1, 4-5, and 10 have been amended and claims 26-29 have been added in the amendment filed 1/22/2007. Claims 1-11 and 26-29 are under examination.

Priority

It is noted that the instant application receives priority to U.S. Provisional Patent application No. 60/550481, filed 3/5/2004. It is noted that the petition for acceptance of an unintentionally delayed claim for priority under 37 CFR 1.178(a)(5) was granted on 2/17/2006. The application receives priority benefit of U.S. Provisional Patent Application No. 60/463,591, filed 4/17/2003.

Claim Objections

Claim 1 has been amended remove the duplication of the word "producing" therefore the objection to claim 1 is withdrawn.

Claim 28 is objected to because of the following informalities: it recites the phrase "wherein the of CD3 to CD28" and it appears that the word "ratio" has been left out of the phrase between the words "the" and "of". For purposes of examination the claim will be interpreted as such. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 has been amended to clarify the claimed method and to remove the indefinite phrase "two steps". The rejection of claims 5-10 under 35 U.S.C. 112, second paragraph related to a method comprising a two step protocol has been withdrawn.

Claims 1-11 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a NEW rejection necessitated by amendment to claim 1.

Claim 1 is vague and indefinite because it recites the phrase "using a lower titer of anti-CD25" and the metes and bounds of "lower titer" is not clear. The specification discloses that a "lower titer" of anti-CD25 magnetic microbeads includes a fraction 1/5th of the manufacturer's recommendation, which appears to be an example or an embodiment of a lower titer and is not a limiting definition. In regards to the disclosed example or embodiment, it is not clear whether the reference to the manufacturer in the specification is referring to the makers of the anti-CD25 mAb themselves (BD PharMingen, see paragraph 0149) or the anti-CD25 microbeads (Miltenyi Biotec). The claim actually recites, "using a lower titer of anti-CD25", not anti-CD25 magnetic microbeads and could be interpreted as a lower titer of antibody instead of anti-CD25 magnetic microbeads. Since the manufacturer's recommended titer is not disclosed in the specification and also it is not clear for what method the manufacturer of the anti-

CD25 had recommended the titer, the skilled artisan would not know what titer would be low enough to meet the limitations of the claimed method.

Claim 1 is also vague and indefinite because it recites the phrase "modified magnetic antibody cell sorting" and it is unclear how the procedure is modified. For example, is the purification procedure modified because it has a lower titer of anti-CD25, or has the procedure been modified in another manner? The skilled artisan would not know what type of modified purification procedure would meet the limitations of the claimed method.

Claims 2-11 and 27-29 are indefinite insofar as they are dependent on indefinite claims.

Claim Rejections - 35 USC § 102 and 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 11 and 26 are rejected under 35 U.S.C. 102(e) as anticipated by Schuler et al (US 2005/0101012) as evidenced by CD25 MicroBeads magnetic cell sorting protocol (pages 1-3), and CD8 Microbead online product literature (page 1), Miltenyi Biotec) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Schuler et al (US 2005/0101012) in view of CD25 MicroBeads magnetic cell sorting protocol (pages 1-3), and in view of CD8 Microbead online product literature (page 1, Miltenyi Biotec). New claim 26 is newly added to this rejection.

Claim 26 recites a method comprising a second generation lineage depletion protocol using two steps, wherein the two steps comprise isolating a population of $CD25^+$ cells from a sample using anti-CD25, and depleting $CD8^+$ cells from the isolated population of $CD25^+$ T cells using anti-CD8 microbeads.

In addition to isolation of $CD25^+$ T cells from a population of $CD4^+$ T cells using CD25 microbeads, as discussed in the previous Office action mailed 7/18/2006, Schuler et al also teach that isolation of $CD8^+$ cells was performed using a negative $CD8^+$ isolation kit made by Miltenyi Biotec (see page 6, paragraph 0077, for example). Product literature from Miltenyi Biotec provides evidence that CD8 MicroBeads are commonly used for direct magnetic labeling of $CD8^+$ cells. Further, Schuler et al teach that in a FACS analysis to confirm the phenotype of the isolated cell population, no contaminating CD8+ cells were observed (see page 7, paragraph 0084, for example).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 7/18/2006) and for reasons outlined below.

Applicants have amended the claims and therefore believe this rejection no longer applies. Applicants submit that Schuler et al must describe each and every element of the claims in order to anticipate these claims under 35 U.S.C. § 102(e), and this reference does not satisfy this requirement. Applicants contend that Examiner is improperly relying on two references in making this rejection (i.e. Shuler and the Miltenyi Biotec CD25 MicroBeads protocol ("the Miltenyi protocol")). In response to the contention by the Examiner that re-eluting the cells over a second column is inherent in view of the Miltenyi protocol, Applicants submit that Schuler does not refer to the Miltenyi protocol. Applicants submit that Schuler cites Miltenyi Biotec for the purpose of providing a source for their kit. Applicants submit that nowhere does Schuler state that the Miltenyi protocol was either followed or modified.

In response to the contention by the Examiner that Schuler does not need to specifically recite a double column purification step because it is inherent in the Miltenyi protocol, Applicants submit that the Miltenyi protocol is an improper citation and therefore cannot be relied on to support this rejection. Applicants submit that nowhere in Schuler alone, inherently or not, is there a disclosure for using a low titer of anti-CD25 in a modified MACS purification procedure. Applicants cite MPEP § 2112 provides: "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flows from the teachings of the prior art (emphasis in original).

Applicants submit that the Examiner has failed to meet the burden established by the MPEP. Schuler does not teach the use of a low titer of anti-CD25. Applicants submit that the Schuler does not inherently teach the presently claimed invention. Applicants submit that the Schuler merely teaches the isolation of $CD25^+$ cells using CD25 MicroBeads. Applicants submit that the Schuler does not even disclose the procedure used to isolate the cells. Rather, Schuler simply makes a reference to the isolation kit of Miltenyi Biotec when describing the source of the kit. Applicants submit that Schuler does not indicate any particular procedure or even whether the procedure was carried out according to manufacturer's protocol or modified in some way. Applicants submit that there exists no fact and/or technical reasoning in Schuler to support the Examiner's contention that re-eluting the cells over a second column is inherent, and the Miltenyi protocol cannot be used to support this rejection.

Applicants submit that the Schuler does not teach a method of using a lower titer of anti-CD25 in a modified MACS purification process comprising a double column purification procedure. The present invention is partly based on the discovery that by performing more stringent purification methodologies, the more potent and reproducible suppressor T cells were isolated. As a result, experiments directed to anti-CD25 MicroBead titration were conducted, which led to the development of the double column purification protocol. Applicants submit that as described in Example 8, using a lower titer of anti-CD25 coated MicroBeads led to isolation of T cells exhibiting more suppressor activity compared to the activity corresponding to T cells isolated using prior art methods.

Applicants submit that without the initial anti-CD25 MicroBead titration experiments, the development of the double column purification procedure would not have been evident. Applicants submit that without the use of the claimed method, a population of T cells with potent suppressor activity or otherwise enhanced suppressive activity would not have been successfully isolated. Applicants further submit that Schuler fails to teach low titers of anti-CD25, and the Miltenyi protocol, even if it was a proper reference, does not cure this deficiency. Applicants contend that using a low titer of anti-CD25 in a modified MACS purification procedure comprising a double column procedure of the present invention is an improvement over prior art methods because such a procedure is a more stringent purification methodology. Applicants further submit that the double column purification procedure is useful in view of the fact that it is advantageous to isolate the $CD25^{bright}$ subset of $CD4^{+}CD25^{+}$ cells in order to detect suppressor activity. This is because it was observed that contaminating of $CD25^{dim}$ cells in $CD25^{+}$ fractions grew faster and can overgrow the $CD25^{bright}$ cells, and thereby preclude the full manifestation of suppressor cell function (See, e.g., Example 8). It was observed that $CD25^{dim}$ cells exhibited a lower suppressive activity than $CD25^{bright}$ cells (See, e.g., paragraph 24, page 8).

Applicant's arguments filed 1/22/2007 have been fully considered but they are not persuasive. It appears that Applicants' arguments are based in part on the amendment to claim 1 introducing the limitation of using a lower titer of anti-CD25 in a modified magnetic antibody cell sorting procedure. Since this limitation is indefinite, it can be given the broadest reasonable interpretation.

Applicants' arguments are also based on whether citation of Miltenyi Biotec by Schuler supports the rejection. Schuler et al reads:

> [0077] $CD4^+$ T cells were isolated from PBMC with a negative $CD4^+$ T cell isolation kit (Miltenyi Biotech). $CD4^+$ $CD25^+$ T cells were isolated from the pure, untouched $CD4^+$ T cells using CD25 Microbeads (Miltenyi Biotech). Isolation of $CD8^+$ T cells was performed using a negative $CD8^+$ T cell isolation kit (Miltenyi Biotech). Purity was assessed by FACS.

Applicants submit that nowhere does Schuler state that the Miltenyi protocol was either followed or modified. While Schuler et al does not specifically refer to the Miltenyi protocol, Schuler et al does disclose that $CD4^+$ $CD25^+$ T cells were isolated using the MicroBeads made by Miltenyi Biotech, and that kits were used to isolate $CD4^+$ T cells and $CD8^+$ T cells. Further, in Example 1, Schuler et al teach that $CD4^+$ cells were magnetically sorted for their expression of CD25 and a 95% pure population of $CD4^+CD25^+$ was obtained by using a MACS CD4 negative selection kit and a positive selection of $CD25^+$ (see paragraph 0081). The skilled artisan would be very likely to use a product as directed by the manufacturer for technical reasons related to the complexity of biotechnology kits, which often require precision in following the method steps for success. Thus, it is reasonable to expect that the method used by Schuler comprises the steps explicitly taught by the Miltenyi Biotech literature or, in the alternative, that it would be obvious to one skilled in the art given the teachings of Schuler to use the process taught by the Miltenyi Biotech literature in order to obtain the full benefit of the kit. There is no teaching to indicate that Schuler et al used a method so different than that described in the Miltenyi Biotec literature for the CD25 MicroBeads (i.e. double column purification procedure) such that the Schuler would have not

repeated the magnetic separation procedure (i.e. double column) using a new column as is directed in step 7 of part 2.3. Absent evidence to the contrary, Schuler et al used CD25 MicroBeads as directed by the Miltenyi Biotec general protocol. Applicants' arguments appear to be partially focused on the novelty of the development of the double column purification protocol to stringently purify suppressor T cells. However, as evidenced by the Miltenyi Biotec commercial protocol of purifying $CD25^+$ cells, repetition of a magnetic separation procedure using a MACS column appears to be a routine step.

The Miltenyi Biotec protocol teaches that various volumes of cells and buffer can be used (see page 2, left column 2.2) and that different amounts of CD25 MicroBeads are used for positive selection or depletion of CD25 cells. The claimed method limitation of a lower titer of anti-CD25 in a modified magnetic cell sorting method can be given the broadest reasonable interpretation. Therefore, the protocol options taught by the Miltenyi Biotec meet the broadest reasonable interpretation of a method comprising the limitation of a lower titer of anti-CD25 in a modified magnetic cell sorting method. Applicants' arguments also focus on the idea that the double column procedure of the instant invention combined with a low titer of antiCD25 in a modified MACS purification is an improvement over prior art methods because such a procedure is a more stringent purification methodology. However, the limitation of lower titer of anti-CD25 is broad and the limitation of high stringency is not recited in the method of claim 1.

Claims 1-3, 5, 11 and 29 are rejected under 35 U.S.C. 102(e) as anticipated by Roncarolo et al (US 2004/0173778) as evidenced by CD25 MicroBead Magnetic

cell sorting protocol (Miltenyi Biotec, pages 1-3) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Roncarolo et al (US 2004/0173778) in view of CD25 MicroBead Magnetic cell sorting protocol (Miltenyi Biotec, pages 1-3). New claim 29 is being added to this rejection.

New claim 29 comprises the limitation that the cells retain long term down regulatory suppressor function for at least three weeks. Roncarolo teaches that the cells were maintained in culture for greater than 14 days while maintaining their proliferative and suppressive capacities (page 2, paragraph 0026 to page 3, paragraph 0028 and Figure 4A). Since suppressor function is maintained the cells for 14 days (two weeks), absent evidence to the contrary, the cells would retain some down regulatory suppressor function for at least three weeks.

This rejection is being maintained for reasons of record in the previous Office Action (mailed 7/18/2006) and for reasons outlined below.

Applicants submit that the deficiencies of Schuler discussed above, although not repeated here, are equally applicable to the instant rejection of claims 1-3, 5 and 11 under 35 U.S.C. §102(e) over Roncarolo. Applicants submit that nowhere does Roncarolo teach using a lower titer of anti-CD25 in a modified MACS purification procedure comprising a double column purification procedure. Applicants submit that similar to Schuler, Roncarolo isolates $CD4^+CD25^+$ T cells by way of a single purification procedure. Applicants submit that nowhere does Roncarolo discuss a cell line that exhibits the potent functional suppressor activity (e.g., >90% inhibition) exhibited by the cells generated from the claimed method. Applicants submit that it appears that

Roncarolo discloses $CD4^+CD25^+$ T cells that are able to inhibit the proliferation of naive CD4 $CD4^+CD25$ T cells by an average of 75%. Applicants submit that not only does Roncarolo not teach the same method of the presently claimed method; Roncarolo also does not arrive at the same cell population generated from using the claimed double column purification procedure.

Applicant's arguments filed 1/22/2007 have been fully considered but they are not persuasive. As discussed above, the claimed method limitation of a lower titer of anti-CD25 in a modified magnetic cell sorting method can be given the broadest reasonable interpretation. The Miltenyi Biotec protocol teaches that various volumes of cells and buffer can be used (see page 2, left column 2.2) and that different amounts of CD25 MicroBeads are used for positive selection of CD25 cells and depletion of CD25 cells. Therefore the protocol options taught by the Miltenyi Biotec meet the broadest reasonable interpretation of a method comprising the limitation of a lower titer of anti-CD25 in a modified magnetic cell sorting method. Applicants' arguments focus on the idea that the double column procedure of the instant invention combined with a low titer of antiCD25 in a modified MACS purification is an improvement over prior art methods because such a procedure is a more stringent purification methodology. However, the limitation of lower titer of antiCD25 is broad and the limitation of high stringency is not recited in the method of claim 1.

Although Applicants submit that, similar to Schuler, Roncarolo isolates $CD4^+CD25^+$ T cells by way of a single purification procedure, Roncarolo is using beads from Miltenyi Biotec, and therefore Roncarolo would be very likely to use the product as

directed by the manufacturer for technical reasons related to the complexity of biotechnology kits, which often require precision in following the method steps for success. Thus, it is reasonable to expect that the method used by Roncarolo comprises the steps explicitly taught by the Miltenyi Biotech literature or, in the alternative, that it would be obvious to one skilled in the art given the teachings of Roncarolo to use the process taught by the Miltenyi Biotech literature in order to obtain the full benefit of the kit. There is no teaching to indicate that Roncarolo et al used a method so different than that described in the Miltenyi Biotec literature so as not to repeat the column purification step as directed in the Miltenyi Biotec protocol.

Applicants submit that nowhere does Roncarolo discuss a cell line that exhibits the potent functional suppressor activity (e.g., >90% inhibition) exhibited by the cells generated from the claimed method. However, the specification does not provide a limiting definition of potent suppressor activity. The instant specification discloses, "As an added advantage, the culture-expanded cells retain potent functional suppressor activity (>95% inhibition, even with dilution to a 1:10 ratio of suppressor cell to responder cell, which rules out potential non-specific causes for suppression)". Further, cells of the invention "are capable of 95% suppression of an MLR" (see instant specification, paragraphs 0027-0028, for example). While Applicants submit that it appears that Roncarolo discloses $CD4^+CD25^+$ T cells that are able to inhibit the proliferation of naive $CD4^+CD25$ T cells by an average of 75%, Roncarolo also discloses that the $CD4^+CD25^+$ cells suppress proliferation of $CD4^+CD25^-$ T cells to immobilized anti-CD3 alone by an average of $79.4\pm14.6\%$ (see paragraph 0038, page 4, for

example), which is ~94% and would meet the limitation of potent suppressor activity. Therefore, absent evidence to the contrary, Roncarolo does teach the same method of the presently claimed method and Roncarolo also does arrive at the same cell population generated from using the claimed double column purification procedure.

Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roncarolo et al (US 2004/0173778) in view of Diehn et al (PNAS (2002) volume 99(18), pages 11796-11801).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 7/18/2006) and for reasons outlined below.

Applicants submit that claims 6-10 ultimately depend from claim 1 and the amendment to claim 1 with respect to a low titer of anti-CD25 in a modified MACS purification procedure comprising a double column purification procedure is an element that must be considered in rejecting claims 6-10. Applicants submit that the deficiencies of Roncarolo discussed above are equally applicable to the instant rejection. Applicants submit that the amendment to claim 1 which encompasses the use of a low titer of anti-CD25 in a modified MACS purification procedure comprising a double column purification procedure renders Roncarolo inapplicable. Applicants submit that therefore, Diehn is required to teach this purification procedure in order to cure the deficiencies of Roncarolo.

Applicants submit that nowhere does Diehn discuss specifically $CD4^+CD25^+$ T cells, let alone methods for producing therapeutic human T regulatory cells with

enhanced suppressive activity. Rather, consistent with the Examiner's reading of Diehn, Diehn is merely a generic teaching of the requirement of both the antigen-specific T cell receptor and a second coreceptor CD28 for optimal activation of T cells. Therefore, Roncarolo in combination with Diehn cannot render the pending claims *prima facie* obvious.

Applicants respectfully submit that this rejection under 35 U.S.C. § 103 is overcome by reliance on the limitation of the double column purification procedure. Applicants submit that nowhere does Diehn disclose a double column purification procedure for isolating T cells. As such, there is no suggestion or motivation for isolating Tregs using a lower titer of anti-CD25 in a modified MACS purification procedure comprising a double column purification procedure as claimed in claim 1. Accordingly, there is no reasonable expectation that a population of therapeutic human Treg cells with enhanced suppressive activity would be generated using the methods disclosed by Diehn or for that matter Roncarolo in combination with Diehn.

In addition, the combined teachings of Ronacarolo and Diehn would teach away from the presently claimed method. Applicants have demonstrated a method for generating a population of Treg cells that exhibit enhanced suppressive activity. Applicants submit that none of the cells disclosed by Ronacarolo and Diehn exhibit this suppressor activity profile. It is also submitted that the enhanced suppressor activity of the cells generated using the double column purification procedure was an unexpected result. This is because if one considers the art as a whole, including the teachings of Ronacarolo and Diehn, one of skill in the art would be lead to believe that a population

of T cells exhibiting potent suppressor activity could not be made using a double column purification. Ronacarolo goes to the level of cloning a population of T cells using limited dilution procedures to generate a relatively pure population. Ronacarolo does not indicate that these clonal population of T cells exhibited the high level of suppressor activity compared to the level observed by Applicants using a double column purification procedure.

Applicant's arguments filed 1/22/2007 have been fully considered but they are not persuasive. The question of the use of a low titer of anti-CD25 in a modified MACS purification procedure comprising a double column purification procedure has been addressed in the discussions above and is applicable to this rejection as well. The issue of whether the cell taught by Roncarolo et al exhibit potent enhanced suppressor activity is addressed above.

Diehn is not required to discuss CD4+CD25+ T cells or do a double column purification procedure for isolating T cells, because they are taught in Roncarolo et al. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is also submitted that the enhanced suppressor activity of the cells generated using the double column purification procedure was an unexpected result. This is because Applicants submit if one considers the art as a whole, including the teachings of Ronacarolo and Diehn, one of skill in the art would be lead to believe that a

population of T cells exhibiting potent suppressor activity could not be made using a double column purification. The instant claims are drawn to methods and can be interpreted with the broadest reasonable interpretation. The instant specification does not provide a limiting definition of an enhanced suppressive activity that would indicate an unexpected result. Therefore, it appears that if the methods of Roncarolo in view of Diehn were followed including a double column purification procedure, the skilled artisan would expect to be able to produce the therapeutic human Treg cells with enhanced suppressive activity, wherein prior to expansion of CD4CD25 suppressor cells would represent a low percentage of the total isolated CD4 T cell population.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 10 and 14 of copending **Application No. 11/226,168**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a method of isolating and expanding CD4÷CD25÷ regulatory T cells. The claims of the instant application do not specifically claim that the Treg cells are phenotypically CD45RA÷, but the specification indicates that the population of CD4÷CD25÷ regulatory T cells isolated and expanded by the claimed method are CD45RA÷ cells (see page 8, paragraph 0025).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants request that the provisional nonstatutory double patenting rejection be placed in abeyance until claims have actually issued or are deemed allowable in one of the applications.

This rejection is being maintained for reasons of record in the previous Office Action (mailed 7/18/2006) but will be placed in abeyance until claims have actually issued or are deemed allowable in one of the applications.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
4/2/2007

DANIEL M. SULLIVAN, PH.D.
PRIMARY EXAMINER